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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/629,074	07/31/2000	RONALD G CRYSTAL	205965	5286

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER

BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/21/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	09/629,074		CRYSTAL ET AL.	
	Examiner		Art Unit	
	Anne Baker		1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12, 17-23 and 25-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 22, 23 and 27 is/are allowed.
- 6) ☒ Claim(s) 1-12, 17-19, 26 and 31 is/are rejected.
- 7) ☒ Claim(s) 20 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input checked="" type="checkbox"/> Other: <i>detailed action</i> |

DETAILED ACTION

The amendment filed August 6, 2002 (Paper No. 12) has been entered. Claims 1, 4, 5, 19, and 22 have been amended. Claims 13-16 and 24 have been cancelled. Claims 26 and 27 have been newly added.

Claims 1-12, 17-23, and 25-27 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 17-21, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering either 1) an adenoviral vector encoding VEGF operably linked to a promoter or 2) an adenoviral vector encoding VEGF and a second osteogenic protein each of which is operably linked to a promoter, to a bone or within a tissue immediately surrounding the bone, whereby bone density or formation is enhanced, does not reasonably provide enablement for administering any type of vector encoding VEGF (and optionally further administering any type of vector encoding an osteogenic protein) to a cell associated with a region of a bone, whereby bone density or formation is enhanced, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Claims 1-12, 17, and 18 are directed to a method for enhancing bone density or formation by administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding a vascular endothelial growth factor (VEGF), such that the first nucleic acid is expressed in the cell to produce the VEGF, whereby bone density or formation is enhanced within the region, wherein the first cell is within the bone or within a tissue immediately surrounding the bone. Claims 19-21 and 26 are directed to a viral vector comprising at least one first nucleic acid encoding a VEGF and at least one second nucleic acid encoding at least one osteogenic protein.

The arguments advanced on pages 5-8 of the Office Action of Paper No. 5 (mailed 4/24/01), on pages 4-6 of the Office Action of Paper No. 7 (mailed 11/23/01), and on pages 3-4 of the Office Action of Paper No. 11 (mailed 6/5/02) are incorporated herein.

The working example of the specification discloses that collagen sponges soaked with a solution of saline and adenoviral vectors encoding either VEGF₁₂₁ or VEGF₁₆₅ were inserted between decorticated spinal bones. New bone formation was observed in 29%, 33%, and 50% of treated sites, depending on the particular protocol.

The specification fails to provide an enabling disclosure for the use of vectors other than adenoviral vectors or for viral vectors as claimed other than adenoviral vectors, because methods of gene therapy are highly unpredictable, for the reasons detailed herein below. The specification does not teach how to use other vectors to achieve enhanced bone density or formation. However, the claims encompass using any type of vector encoding VEGF, as well as any type of vector encoding an osteogenic protein.

The claimed invention is directed to methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods and compositions with specific guidance. However, the specification fails to adequately teach a method for using a VEGF-encoding vector other than an adenoviral vector to transfer a VEGF gene to a target cell and express the VEGF gene at a level sufficient to achieve the claimed effect, i.e. enhanced bone density

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or formation. The specification does not provide specific guidance for the use of other gene transfer vectors, particularly with regard to targeted gene delivery, the route and time course of administration, when, where, or for how long the VEGF gene should be expressed, the frequency of administration of the gene therapy vector, or in some embodiments, the intended target tissue, for enhancing bone density and formation in an immunocompetent animal. The specification also lacks working examples showing that vectors other than adenoviral vectors could be used to deliver the VEGF gene to the appropriate site, and that once delivered the VEGF gene would be expressed at a level sufficient to provide adequate product to effect the desired therapy in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...", and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods with vectors other than adenoviral vectors. Thus, absent any showing that other vectors can be used to produce the intended therapeutic effect in an immunocompetent animal, such as a human, the claimed methods and compositions are not enabled by the disclosure over the full scope. As gene therapy is not routine for

the reasons discussed herein, undue experimentation would have been required for one skilled in the art to practice the claimed method using vectors other than adenoviral vectors.

The specification fails to provide an enabling disclosure for targeting appropriate cells using vectors other than adenoviral vectors. Only general guidance is offered with regard to targeting strategies known in the art. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem, such that a wide variety of vector types, including both viral and non-viral vectors, could be used to enhance bone density or formation. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that “for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems” (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the “ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time” (page 53, first paragraph). Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that “among the design hurdles for all

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vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated” (page 409).

Even expression studies in animals are often not predictive that the same or similar results can be achieved in patients or that such expression would alleviate clinical symptoms. For example, although researchers have demonstrated expression of the CFTR gene in the surface airway cells of laboratory animals, problems transferring sufficient quantities of the CFTR gene into patients' cells have prevented the method from providing therapeutic benefit. Furthermore, the viral vector used to transfer the gene provoked an immune reaction in some patients (Marshall, 1995, p. 1052). Marshall emphasizes that the central challenge in the field of gene therapy is to find safe vectors capable of transporting genes efficiently into target cells, and getting the cells to express the genes once they are inserted. These problems remain unresolved.

In view of the quantity of experimentation necessary to determine appropriate parameters for practicing the claimed method with other vectors to achieve enhanced bone density or formation in immunocompetent animals, and given the limited applicable working examples directed exclusively to the use of adenoviral vectors, the limited guidance in the specification with regard to the implementation and design of other vectors, the broad scope of the claims with regard to the type of vector to be used, and the unpredictability in the gene therapy art, undue experimentation would have been required for one skilled in the art to practice the claimed method over the full scope and use the claimed compositions over the full scope.

The rejection of Claims 19-21 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5, 942,496 (Bonadio et al., 8/24/99) is withdrawn in view of the amendments to the claims. The claims are now limited to a viral vector comprising at least one first nucleic acid encoding **VEGF** and at least

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one second nucleic acid encoding at least one osteogenic protein. Thus, the claims no longer cover a viral vector encoding FGF in combination with PTH or BMP.

Conclusion

Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 22, 23, 25, and 27 are allowable. Claims 22, 23, 25, and 27 are directed to a bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding a VEGF and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein.

The claims are free of the prior art of record.

Claims 1-12, 17-21, and 26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER